Postmarketing Safety Profile of Subcutaneous Interferon Beta-1a Given 3 Times Weekly: A Retrospective Administrative Claims Analysis

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ABSTRACT

BACKGROUND: Health insurance administrative claims databases represent a valuable source of information regarding the safety profile of marketed products as used in actual clinical practice in a broader range of patients than that assessed in clinical trials. Interferon beta-1a administered subcutaneously 3 times weekly (IFN β -1a SC tiw), which was approved in 2002 by the FDA for the treatment of relapsing-remitting multiple sclerosis (MS), has over a decade of postmarketing experience. To date, however, its postmarketing safety profile has not been described using a real-world evidence source such as administrative claims data.

OBJECTIVE: To describe the safety profile of IFN β -1a SC tiw as presented in its U.S. prescribing information (PI) for patients with MS initiating IFN β -1a SC tiw therapy using data from U.S. health care administrative claims databases.

METHODS: This study featured an observational and retrospective “new start” cohort design using data from the Truven MarketScan Commercial and Medicare Supplemental health care administrative claims databases. Patients were eligible for inclusion if they were aged ≥ 18 years; had ≥ 1 diagnosis for MS recorded between January 1, 2006, and December 31, 2012; had ≥ 2 prescriptions for IFN β -1a SC tiw; and had ≥ 90 days of continuous eligibility pre-index date and ≥ 180 days of continuous eligibility post-index date. Patients with a prescription for IFN β -1a SC tiw without a MS diagnosis were excluded. Patients were followed from first prescription for IFN β -1a SC tiw (index date) until date of therapy switch or discontinuation, end of insurance eligibility, or end of observation period. Adverse events (AEs) examined were those listed in the Warnings and Precautions, Adverse Reactions, and Postmarketing Experience sections of the 2014 U.S. PI. Outcomes of interest were identified at the Medical Dictionary for Regulatory Activities (version 17.1) Preferred Term level and then coded to the corresponding ICD-9-CM criteria. Descriptive analyses of patient demographic, health status, health care utilization, and adherence status were performed, and incidence rates (IRs) per 100 person-years of labeled AEs with corresponding 95% CIs were calculated. The IR calculation was based on events that presented after therapy initiation and that were not present in the 90-day pre-index period.

RESULTS: The top 6 AEs included influenza-like symptoms (IR = 15.65, 95% CI = 14.96-16.36); malaise (IR = 15.33, 95% CI = 14.65-16.04); fatigue (IR = 15.02, 95% CI = 14.35-15.72); abdominal pain (IR = 10.18, 95% CI = 9.67-10.70); chest pain (IR = 8.48, 95% CI = 8.03-8.95); and depression (IR = 7.75, 95% CI = 7.32-8.20). In contrast, the 6 lowest IRs were for maculo-papular rash (IR = 0.01, 95% CI = 0.00-0.04); injection-site necrosis (IR = 0.01, 95% CI = 0.00-0.03); erythema multiforme (IR = 0.01, 95% CI = 0.00-0.04); hypoesthesia (IR = 0.00, 95% CI = 0.00-0.02); Stevens-Johnson Syndrome (IR = 0.00, 95% CI = 0.00-0.02); and xerophthalmia (IR = 0.00, 95% CI = 0.00-0.02).

CONCLUSIONS: Study results show strong convergence between the real-world safety profile of IFN β -1a SC tiw and its U.S. label. Our findings demonstrate the value of using real-world evidence obtained from administrative claims to complement clinical trial and postmarketing surveillance data in order to characterize the safety profile of established products, such as IFN β -1a SC tiw, in the postmarketing context.

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What is already known about this subject

- Although interferon beta-1a administered subcutaneously 3 times weekly (IFN β -1a SC tiw) was approved in the United States in 2002 as a first-line therapy for the treatment of relapsing-remitting multiple sclerosis, its safety profile has been established primarily in pre- and postauthorization clinical trials and postmarketing surveillance—sources that may not adequately represent the context of real-world clinical care and the broader range of patients treated in actual practice.
- The most commonly reported adverse events (AEs) associated with IFN β -1a SC tiw in controlled clinical trials include injection site disorders, influenza-like symptoms, abdominal pain, depression, headache, elevation of liver enzymes, and hematologic abnormalities.

What this study adds

- This study is unique because it describes the safety profile of IFN β -1a SC tiw as characterized in its U.S. prescribing information, using real-world data from a large, longitudinal, and geographically diverse U.S. health care administrative claims dataset.
- Study results show strong convergence between the real-world safety profile of IFN β -1a SC tiw and its U.S. label. The relative frequency of adverse events seen in the administrative claims dataset was comparable with that reported in pivotal trials.

Multiple sclerosis (MS) is a chronic and progressively debilitating condition that affects the central nervous system.¹ Worldwide, the disease is estimated to affect approximately 2.1 million individuals.¹ During the initial disease course, approximately 85% of patients develop

relapsing neurological symptoms, a condition referred to as relapsing-remitting MS (RRMS). While disease course and rate of progression vary widely, common symptoms of MS include numbness or paresthesia, impaired motor coordination, visual problems, bladder and bowel dysfunctions, sexual and cognitive dysfunction, and fatigue.²

Currently, various disease-modifying drugs (DMDs) are recognized as first-line therapy for RRMS. Prominent among these are the interferon betas (IFN β s), a class of injectable products that features intramuscular (IM; Avonex [IFN β -1a IM], 30 micrograms [μ g] once weekly) and subcutaneous options (SC; Rebif [IFN β -1a SC], 22 μ g or 44 μ g 3 times weekly [tiw]; Betaseron [IFN β -1b SC], 250 μ g every other day; and Plegridy [peg-interferon β -1a SC], 125 μ g every 2 weeks). While typically well tolerated, certain class effects of IFN β s include anemia; aminotransferase elevations; skin reactions (e.g., injection site redness, swelling, and pain); and neutralizing antibodies.^{2,3}

Of these IFN β products, interferon beta-1a administered subcutaneously 3 times weekly (IFN β -1a SC tiw) is one of the most widely prescribed, with over 15 million doses sold since its approval by the U.S. Food and Drug Administration (FDA) in 2002.⁴ The effectiveness and safety of IFN β -1a SC tiw have been well established in clinical trials.^{5,6}

To date, the U.S. label information on the safety profile of IFN β -1a SC tiw has been derived predominantly from pivotal randomized controlled clinical trials and postmarketing surveillance.^{5,6} The most common adverse events (AEs) seen in controlled clinical trials were injection site disorders, influenza-like symptoms, abdominal pain, depression, elevation of liver enzymes, and hematologic abnormalities.^{5,6}

Controlled clinical trials and postmarketing surveillance, however, have known biases with regard to drug-related safety information and the degree to which they are representative of “real-world” patients and clinical care practice. Trials conducted as part of clinical development are statistically powered to demonstrate superior efficacy, as opposed to safety, against placebo and are of limited duration and size. Moreover, clinical trial participants represent only a small, highly selective segment of the target patient population and receive treatment and follow-up under tight study protocols and closely monitored conditions. Similarly, postmarketing safety surveillance data, which rely on passive voluntary reporting methods, is limited by substantial underreporting.⁷

While numerous postmarketing, noninterventional observational studies involving IFN β -1a SC tiw have been conducted, most have focused on drug effectiveness or adherence as opposed to safety.⁸⁻¹³ Others have focused on only 1 AE,^{14,15} have had small sample sizes, or have featured relatively short follow-up periods (< 2 years).¹⁶⁻²⁰ The limited follow-up periods are of particular concern given that MS is a disease characterized by a progressive course that typically spans many years.²

More recently, several open-label, longitudinal, observational studies of patients with RRMS treated with IFN β s, including IFN β -1a SC tiw, have reported data on a limited set of AEs associated with the use of these products.²¹⁻²³ Such AEs included influenza-like symptoms, skin or injection problems, depression, headache, injection-site pain, fatigue, pyrexia, myalgia, transaminase level increased, pain in extremity, and liver function test abnormality.²¹⁻²³

One untapped source of long-term, real-world safety information on IFN β -1a SC tiw patients is that found in large health care insurer/payer claims datasets. Administrative claims datasets contain longitudinal information on patient prescription drug history, safety outcomes, and health care utilization in actual clinical care settings and the broader patient population and can be used to describe a range of AEs, despite the fact that some miscoding can occur. Notably, these claims datasets are increasingly being used by the FDA as part of its Sentinel Initiative to monitor the safety profile of drug products in a timely manner under real-world use conditions.²⁴

The objective of this study was to describe the safety profile of IFN β -1a SC tiw as presented in its U.S. prescribing information (PI), in a general MS population initiating IFN β -1a SC tiw therapy.

Methods

Data Source

This retrospective cohort study was conducted utilizing data from the Truven MarketScan Commercial and Medicare Supplemental health care claims databases for the period between January 1, 2006, and December 31, 2012. The databases include information from commercial health insurance claims (inpatient and outpatient medical and outpatient pharmacy) and enrollment data from large employers and health plans across the United States. The MarketScan Medicare Supplemental and Coordination of Benefits (Medicare) database contains the inpatient medical, outpatient medical, and outpatient prescription drug information of retirees with Medicare supplemental insurance paid for by employers. These databases provide detailed cost, use, and outcomes data for health care services performed in inpatient and outpatient settings. The medical claims are linked to outpatient prescription drug claims and person-level enrollment data through the use of unique enrollee identifiers.

These databases are fully compliant with the Health Portability and Accountability Act of 1996 (HIPAA), meet the criteria for a limited-use dataset and contain none of the data elements prohibited by HIPAA for limited-use datasets. All data are de-identified to protect the privacy of patients and providers. Accordingly, institutional review board and ethics committee approval were not required for the study.

Overall, MarketScan covered approximately 158 million patients from 2000 to 2012. For the year 2012, it included

approximately 51 million eligible subjects. The regional representation of this commercial claims database in the United States is as follows: Northeast, 5.44%; North Central, 23.05%; South, 38.61%; West, 19.89%; and Unknown, 2.98%. Medicare does not track patients' regions. In the period from 2000 to 2012, 85.3% of the subjects included in the database were commercially insured, and 6.5% belonged to Medicare (n = 10,459,149). Codes used in MarketScan are *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes for disease, Current Procedural Terminology/Healthcare Common Procedure Coding System codes, and National Drug Code numbers for drugs.

Study Design

This study was observational and retrospective with a “new start” design. “New start” refers to initial inception of patients onto IFN β -1a SC tiw therapy as measured by no pharmacy claims for IFN β -1a SC tiw in the 90 days prior to the index date. Outcomes included the AEs described in the U.S. PI for IFN β -1a SC tiw in the Warnings and Precautions, Adverse Reactions, and Postmarketing Experience sections.²⁵

Study Sample

The study sample consisted of patients aged ≥ 18 years with evidence of MS (≥ 1 medical claims associated with a primary diagnosis of MS (ICD-9-CM 340.XX) and ≥ 2 prescription claims for IFN β -1a SC tiw after the ICD-9-CM 340.XX diagnosis) during the study period January 1, 2006, to December 31, 2012. In addition, eligible patients were required to have no prior record of IFN β -1a SC tiw treatment in the database history, a minimum of 90 days of continuous eligibility prior to IFN β -1a SC tiw treatment initiation, and a minimum of 180 days of continuous eligibility after IFN β -1a SC tiw treatment initiation. No power calculation was required, since the study was descriptive in nature and not designed to test specific hypotheses.

Variables

Exposure Measurement. The index date was defined as date of the first IFN β -1a SC tiw prescription following an MS diagnosis. All outcomes were measured during the period following the index date. Patients were followed from index date until date of therapy switch or discontinuation, end of observation period (i.e., December 31, 2012), or end of insurance eligibility (censor date). Patients could experience more than 1 event and could be counted for 1 or more AEs. The list of codes for each DMD is displayed in Appendix A (available in online article).

Patient Characteristics. Baseline characteristics included patient demographics and health status. Postbaseline health care utilization, relapse rate, dose, and treatment adherence were also described.

Patient demographics and health status were recorded at the time of the index prescription claim. These variables included sex, age (years), history of other DMDs (yes/no), Charlson Comorbidity Index (CCI) score at baseline (mean and standard deviation [SD]),²⁶ and annualized relapse rate. Relapses were calculated using a validated algorithm that defined a MS-related relapse as consisting of either (a) a claim with an MS diagnosis in the primary position at any time during an inpatient hospitalization or (b) a claim with an MS diagnosis code in the primary or secondary position in an outpatient setting (including emergency room visits) in addition to a pharmacy or medical claim for a qualifying corticosteroid on the day of, or within 7 days after, the visit.^{27,28}

Health care utilization was measured in terms of number of inpatient hospitalizations and emergency room admissions. Prior DMD use and comedication use (concomitant corticosteroid use: yes/no), adherence status, and average length of time on therapy were also assessed.

Treatment adherence was operationalized as the number of days of medication supplied within a refill interval in relation to the number of days in the refill interval, also referred to as the medication possession ratio (MPR).²⁹ The MPR was calculated using the following formula: total prescription days of supply divided by [(last prescription fill date minus first prescription fill date) plus (last prescription day of supply)].

The MPR was reported as a percentage, with a cutoff of 80% or above defined as being adherent.

Endpoints Collected

Endpoints assessed included the incidence rates (IRs) for the AEs listed in the Warnings and Precautions, Adverse Reactions, and Postmarketing Experience sections of the April 2014 U.S. PI for IFN β -1a SC tiw.²⁵ An event of interest was defined as any sign or medical diagnosis recorded in the database that started any time after the index date.

Outcomes of interest for this study were described at the Medical Dictionary for Regulatory Activities (MedDRA, version 17.1) Preferred Term (PT) level for individual events and further categorized into system organ classes and then coded with corresponding ICD-9-CM codes (see Appendix B, available in online article).

Data Analysis

The study data were analyzed using SAS 9.4 (SAS Institute, Inc., Cary, NC). A descriptive profile of study participants by adherence status was conducted in terms of demographics; health status (e.g., comorbid conditions and relapse rate); prior DMDs; health care utilization; mean number of days of IFN β -1a SC tiw usage; and IRs of specified AE endpoints. Frequency distributions were provided for categorical variables, and mean (SDs) were provided for continuous variables.

We conducted 3 sets of analyses in accordance with the 3 key safety information sections of the U.S. PI for IFN β -1a

Postmarketing Safety Profile of Subcutaneous Interferon Beta-1a Given 3 Times Weekly: A Retrospective Administrative Claims Analysis

TABLE 1 Characteristics of Study Participants^a

Variable	Study Participants (N=8,107)
Sex, n (%)	
Male	1,932 (23.8)
Female	6,175 (76.2)
Age, mean (SD)	43.1 (10.7)
Charlson Comorbidity Index	
Mean (SD)	0.5 (1.1)
Index=0, n (%)	5,809 (71.7)
Index=1, n (%)	1,302 (16.1)
Index=2, n (%)	581 (7.2)
Index≥3, n (%)	415 (5.1)
Relapses per year, mean (SD)	0.21 (0.48)
Health care utilization, n (%)	
≥1 ER visits	2,932 (36.2)
≥1 hospitalizations	1,649 (20.3)
Corticosteroid use, n (%)	
Yes	2,865 (35.3)
No	5,242 (64.7)
Prior DMD use, n (%)	
Yes	2,466 (30.4)
No	5,641 (69.6)
Days observed on IFN β-1a SC tiw, mean (SD)	554.2 (526.8)

^aThe following variables reflect patient status at index date: sex, age, prior DMD use, and Charlson comorbidity status. The following variables reflect patient status over the course of the study period: number of ER and hospital visits, corticosteroid use, mean days observed on therapy, and mean number of relapses.

DMD = disease-modifying drug; ER = emergency room; IFN β-1a SC tiw = interferon beta-1a administered subcutaneously 3 times weekly; SD = standard deviation.

TABLE 2 Incidence Rates Per 100 Patient-Years and 95% Confidence Intervals for Adverse Events Listed in Warnings and Precautions Section of IFN β-1a SC tiw Prescribing Information

Adverse Event	Study Participants (N=8,107) IR (95% CI)
Psychiatric disorders	
Depression	7.75 (7.32-8.20)
Suicide	0.00 (0.00-0.02)
Suicidal ideation	0.19 (0.14-0.27)
Suicide attempt	0.03 (0.01-0.07)
Hepatic injury	
Hepatic failure	0.06 (0.03-0.10)
Jaundice	0.07 (0.04-0.11)
SGPT increased	1.52 (1.35-1.70)
SGOT increased	1.26 (1.11-1.43)
Severe liver injury	1.09 (0.95-1.25)
Hepatic function abnormal	0.50 (0.41-0.61)
Immune system disorder	
Anaphylactic reactions	0.13 (0.08-0.19)
Skin and subcutaneous tissue disorders	
Urticaria	0.95 (0.82-1.10)
Central and peripheral nervous system disorders	
Seizures	1.72 (1.54-1.92)
Blood and the lymphatic system disorders	
Leukopenia	0.82 (0.70-0.96)
Endocrine disorders	
Thyroid disorder	5.08 (4.74-5.44)
Hypothyroidism	3.60 (3.32-3.90)
Hyperthyroidism	0.52 (0.42-0.63)

CI = confidence interval; IFN β-1a SC tiw = interferon beta-1a administered subcutaneously 3 times weekly; IR = incidence rate; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

SC tiw. IRs per 100 patient-years (PYs) with 95% confidence intervals (CIs) were calculated for each AE separately. To calculate the IR, the numerator was the number of patients who developed the outcome (the specifically labeled AE) following the index date of IFN β-1a SC tiw exposure and for whom that event had not been present in the 90-day pre-index period. Person time was defined as beginning at index date and ending at treatment switch or discontinuation, end of insurance eligibility, or end of study period. The IR was calculated as the number of patients with an event during the post-index follow-up period divided by the total person time accrued by the population during the follow-up. The follow-up range was between index date and censor date.

Results

The database contained 285,476 patients with diagnoses of MS from 2006 to 2012 (eligible subjects). In the same time period, 14,135 patients initiated IFN β-1a SC tiw therapy following MS diagnosis. Of these, 8,107 patients were aged ≥18 years when starting IFN β-1a SC tiw and had at least 90 days of continuous eligibility prior to index date and at least 180 days of continuous eligibility post-index date (sample size).

Patient Characteristics

A description of patient characteristics is presented in Table 1. Results show that the majority of study participants were female (76.2 %) and had a mean (SD) age of 43.1 (10.7) years. Regarding health status, a majority of patients had a CCI score of 0 or less (71.7%). Mean (SD) annual relapse rate was 0.21 (0.48) throughout the study duration. In terms of health care utilization, approximately one-third (36.2%) had 1 or more emergency room visits, and approximately one-quarter (20.3%) had 1 or more hospitalizations during the study period for all causes. In terms of comedications, approximately one-third (35.3%) were using corticosteroids at the point of IFN β-1a SC tiw initiation; similarly, approximately one-third (30.4%) had used another DMD prior to initiating IFN β-1a SC tiw therapy. The mean (SD) length of time on IFN β-1a SC tiw was 554.2 (526.8) days.

Of the 8,107 study participants, 33.0% (n=2,677) met criteria for being continuously adherent on IFN β-1a SC tiw; 16.2% (n=1,316) remained on IFN β-1a SC tiw but were not

**Postmarketing Safety Profile of Subcutaneous Interferon Beta-1a Given 3 Times Weekly:
A Retrospective Administrative Claims Analysis**

TABLE 3 Incidence Rates Per 100 Patient-Years and 95% Confidence Intervals for Adverse Events Listed in Adverse Reactions Section of IFN β -1a SC tiw Prescribing Information^a

Adverse Event	Study Participants (N=8,107) IR (95% CI)
General disorders and influenza-like symptoms	
Influenza-like symptoms	15.65 (14.96-16.36)
Headache	6.94 (6.52-7.38)
Fatigue	15.02 (14.35-15.72)
Pyrexia	2.65 (2.42-2.89)
Rigors	1.29 (1.13-1.46)
Chest pain	8.48 (8.03-8.95)
Malaise	15.33 (14.65-16.04)
Injection-site disorders	
Injection-site necrosis	0.01 (0.00-0.03)
Injection-site reaction	0.03 (0.01-0.07)
Central and peripheral nervous system disorder	
Hypertonia	0.23 (0.16-0.30)
Coordination abnormal	2.08 (1.88-2.30)
Convulsions	1.38 (1.22-1.56)
Endocrine disorders	
Thyroid disorder	5.08 (4.74-5.44)
Gastrointestinal disorders	
Abdominal pain	10.18 (9.67-10.70)
Dry mouth	0.12 (0.08-0.18)
Hepatobiliary disorders	
Hepatic function abnormal	0.50 (0.41-0.61)
Bilirubinemia	0.02 (0.01-0.05)
Musculoskeletal and connective tissue disorders	
Myalgia	3.11 (2.86-3.38)
Back pain	4.16 (3.87-4.48)
Skeletal pain	0.35 (0.27-0.44)
Hematologic disorders	
Lymphadenopathy	1.16 (1.01-1.32)
Thrombocytopenia	0.54 (0.44-0.65)
Anemia	6.25 (5.88-6.65)
Psychiatric disorders	
Somnolence	1.11 (0.96-1.27)
Skin and subcutaneous tissue disorders	
Rash, erythematous	1.20 (1.05-1.37)
Rash, maculo-papular	0.01 (0.00-0.04)
Renal and urinary disorders	
Micturition frequency	3.50 (3.24-3.79)
Urinary incontinence	3.13 (2.87-3.39)
Eye disorders	
Vision abnormal	4.04 (3.74-4.36)
Xerophthalmia	0.00 (0.00-0.02)

^aList of adverse reactions does not include those already presented in Table 2 (i.e., psychiatric disorders [depression, suicide], seizures, hepatobiliary disorders, and leukopenia).

CI=confidence interval; IFN β -1a SC tiw=interferon beta-1a administered subcutaneously 3 times weekly; IR=incidence rate.

consistently adherent during the study period; 24.3% (n=1,972) switched at one point to another DMD; and 26.4% (n=2,142) discontinued therapy at one point and did not initiate treatment on another DMD during the study period.

IRs of Adverse Reactions Included in Warnings and Precautions Section

Table 2 presents IRs and 95% CIs per 100 PYs for adverse reactions listed in the Warnings and Precautions section of the U.S. PI for IFN β -1a SC tiw. For all study participants, the highest IRs included depression (IR=7.75, 95% CI=7.32-8.20); thyroid disorder (IR=5.08, 95% CI=4.74-5.44); hypothyroidism (IR=3.60, 95% CI=3.32-3.90); seizures (IR=1.72, 95% CI=1.54-1.92); increased serum glutamic pyruvic transaminase (SGPT) levels (IR=1.52, 95% CI=1.35-1.70); increased serum glutamic oxaloacetic transaminase (SGOT) levels (IR=1.26, 95% CI=1.11-1.43); and severe liver injury (IR=1.09, 95% CI=0.95-1.25). In contrast, IRs for injection-site reaction and injection-site necrosis were among the lowest reported (IR=0.03, 95% CI=0.01-0.07 and IR=0.01, 95% CI=0.00-0.03, respectively; Table 3).

IRs of Adverse Reactions Included in Adverse Reactions Section

Table 3 presents IRs and 95% CIs per 100 PYs for events listed in the Adverse Reactions section of the U.S. PI for IFN β -1a SC tiw. The highest rates were for influenza-like symptoms (IR=15.65, 95% CI=14.96-16.36); malaise (IR=15.33, 95% CI=14.65-16.04); fatigue (IR=15.02, 95% CI=14.35-15.72); abdominal pain (IR=10.18, 95% CI=9.67-10.70); chest pain (IR=8.48, 95% CI=8.03-8.95); and headache (IR=6.94, 95% CI=6.52-7.38).

IRs of Adverse Reactions Included in Postmarketing Section

Table 4 presents IRs and 95% CIs per 100 PYs for AEs listed in the Postmarketing Experience section of the U.S. PI for IFN β -1a SC tiw. The IRs for autoimmune disorders were 0.25 (95% CI=0.19-0.33) for drug-induced lupus erythematosus and 0.04 (95% CI=0.01-0.07) for autoimmune hepatitis.

In terms of blood and lymphatic system disorders, the IR for thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome (TTP/HUS) was 0.63 (95% CI=0.53-0.75), and the IR for pancytopenia was 0.10 (95% CI=0.06-0.16). In terms of eye disorders, the IRs ranged from 0.04 (95% CI=0.01-0.07) for obstruction of retinal artery or vein to 0.40 (95% CI=0.31-0.50) for retinopathy.

The highest IRs in the Postmarketing Experience section were reported for central and peripheral nervous system disorders, including paresthesia (IR=6.69, 95% CI=6.25-7.16); muscle spasms (IR=3.31, 95% CI=3.05-3.58); and difficulty walking (IR=1.85, 95% CI=1.66-2.06). In contrast, the IR for hypoaesthesia was 0.00 (95% CI=0.00-0.02).

Postmarketing Safety Profile of Subcutaneous Interferon Beta-1a Given 3 Times Weekly: A Retrospective Administrative Claims Analysis

TABLE 4 Incidence Rates Per 100 Patient-Years and 95% Confidence Intervals for Adverse Events Listed in Postmarketing Experience Section of IFN β -1a SC tiw Prescribing Information^a

Adverse Event	Study Participants (N=8,107) IR (95% CI)
Autoimmune disorders	
Drug-induced lupus erythematosus	0.25 (0.19-0.33)
Autoimmune hepatitis	0.04 (0.01-0.07)
Blood and the lymphatic system disorders	
TTP/HUS	0.63 (0.53-0.75)
Pancytopenia	0.10 (0.06-0.16)
Eye disorders	
Retinopathy	0.40 (0.31-0.50)
Cotton wool spots	0.27 (0.20-0.35)
Obstruction of retinal artery or vein	0.04 (0.01-0.07)
Central and peripheral nervous system disorder	
Hypoesthesia	0.00 (0.00-0.02)
Muscle spasms	3.31 (3.05-3.58)
Parasthesia	6.69 (6.25-7.16)
Musculoskeletal stiffness	0.72 (0.60-0.85)
Difficulty walking	1.85 (1.66-2.06)
Skin and subcutaneous tissue disorders	
Erythema multiforme	0.01 (0.00-0.04)
Stevens-Johnson syndrome	0.00 (0.00-0.02)
Injection-site abscess	1.71 (1.53-1.91)
Injection-site cellulitis	1.71 (1.53-1.91)
Injection-site necrosis	0.01 (0.00-0.03)

^aList of postmarketing adverse events does not include those already presented in Table 2 (i.e., psychiatric disorders [depression, suicide], seizures, and hepatobiliary disorders).

CI=confidence interval; IFN β -1a SC tiw=interferon beta-1a administered subcutaneously 3 times weekly; IR=incidence rate; TTP/HUS=thrombotic thrombocytopenic purpura/hemolytic uremic syndrome.

Among skin and subcutaneous tissue disorders, the highest IRs were for injection-site abscess and injection-site cellulitis (IR=1.71, 95% CI=1.53-1.91 for both). In contrast, the lowest IRs were seen for erythema multiforme, Stevens-Johnson Syndrome, and injection-site necrosis (IR=0.01, 95% CI=0.00-0.04; IR=0.00, 95% CI=0.00-0.02; and IR=0.01, 95% CI=0.00-0.03, respectively).

Discussion

Our retrospective analysis provides real-world, longitudinal information regarding safety outcomes listed in the Warnings and Precautions, Adverse Reactions, and Postmarketing Experience sections of the U.S. PI for IFN β -1a SC tiw. A major strength of this study is that it reflects patients with MS receiving care under real-world clinical practice conditions across different geographic regions in the United States. Overall, our results show a safety profile that is consistent with the relative frequency of AEs listed in the U.S. label for IFN β -1a SC tiw.

Our study findings show that the highest AE IRs were for AEs of mild-to-moderate nature and were assumed to be clinically manageable. In particular, the highest reported IRs were for influenza-like symptoms, fatigue, malaise, and chest pain. In the clinical trial results in the U.S. PI, influenza-like symptoms are listed as the second most frequently occurring AE (56% and 59% for IFN β -1a 22 μ g and 44 μ g SC tiw doses, respectively). Other postmarketing studies have shown influenza-like symptoms to be a common AE associated with IFN β therapy.^{21-23,30,31} Typically, these symptoms have been shown to abate, in terms of frequency and severity, with increased time on treatment. In particular, clinical trial results showed that 69% of patients reported influenza-like symptoms over the course of 1 to 4 years, but only 12% did so after up to 8 years of follow-up.^{32,33} Similarly, in a postmarketing observational registry study, the incidence of influenza-like symptoms for patients taking IFN β -1a 22 μ g and 44 μ g SC tiw ranged from 31.4% to 33.3%, respectively, at 3 months versus 8.9% and 3.3%, respectively, at 12 months.²¹ Fatigue and malaise are common symptoms associated with MS, with up to 90% of patients with MS reporting fatigue.²

In the controlled clinical trials and long-term follow-up studies for IFN β -1a SC tiw, the most commonly reported AEs were injection-site disorders.^{4,5,23} While injection-site disorders are commonly reported AEs for injectable IFN β formulations in general (particularly those administered SC), our results showed low IRs for this AE.¹⁴ In a 2011 study by Beer et al. (2011), the reported rates of injection-site reactions ranged from 57.7% for IFN β -1b SC to 67.9% for IFN β -1a SC tiw.¹⁴ In our analysis, the low IRs for injection-site reactions may possibly be a function of clinician undercoding due to the relatively mild clinical nature of this event. Given the fact that the drug is self-administered in the home setting, many of these events may resolve spontaneously and relatively quickly, thus, negating the need to see a health care professional. In addition, patients who have been using an injectable drug may have become accustomed to injection-site reactions and may not even perceive them to be worth mentioning to a health care professional. Further support for this interpretation is evident in results from 1 of the IFN β -1a SC tiw pivotal trials in which physicians rated the injection-site disorders as being mild in the vast majority of cases (in 84% of the high-dose cases and in 92% of the low-dose cases).⁵

In terms of more serious AEs, we found much lower IRs. In particular, the IR for depression was approximately half of that for influenza-like symptoms (IR of 7.75 vs. 15.65, respectively) while those for suicidal ideation, suicide attempt, and suicide were comparatively even lower (IRs of 0.19, 0.03, and 0.00, respectively). Depression is a commonly reported symptom for patients with MS in general, and cases of depression in patients receiving IFN β -1a SC tiw have been linked to preexisting depressive symptoms.^{2,34,35} Additionally, depression, suicidal

ideation, and suicide attempts have all been observed with increased frequency in patients using IFN compounds.²⁵

Hepatic injury was most commonly reported in terms of increased liver enzyme levels, while the incidence of more serious events, including liver injury and hepatic failure, was notably lower. In 2 systematic reviews examining hepatic dysfunction in patients receiving IFN β -1a SC tiw that used data from randomized controlled clinical trials and postmarketing surveillance studies, raised hepatic aminotransferase levels were predominately asymptomatic, tended to occur early (within the first 12 months) in treatment, and often were resolved spontaneously or with dosage adjustment.^{36,37}

Other serious AEs, including Stevens-Johnson syndrome, TTP/HUS, drug-induced lupus erythematosus, autoimmune hepatitis, and urticaria, showed uniformly low IRs. Rio et al. (2005), in an 8-year follow-up study of IFN β patients, found 3 cases of urticaria and angioedema in those taking IFN β -1a SC tiw.⁹

A strength of our study is that it aimed to reflect real-world use of IFN β -1a SC tiw. Consistent with real-world usage, patients varied in terms of the degree of adherence to IFN β -1a SC tiw. For the purposes of AE calculations, we included all patients who had been exposed to the product, not just those who were highly compliant.

An array of disease management strategies have been developed for many of the most common AEs reported here, including injection-site disorders, depression, and influenza-like symptoms. Care provided by multidisciplinary teams of health care professionals in conjunction with support services, such as nurse-staffed patient support call centers, offer patients access to information and advice on management of symptoms, side effects, and comorbidities. These services can be effective in mitigating AEs and assisting patients in being adherent, thereby optimizing treatment benefits while reducing treatment-related risks.³¹

Limitations

There are some limitations to the study associated with the use of commercial health care claims databases.³⁸ Administrative health care claims data do not include clinical information (e.g., laboratory values and disease severity) or other measures (e.g., socioeconomic status) that could affect study outcomes. The ICD-9-CM code for systemic MS does not distinguish among different MS types (e.g., primary progressive MS, RRMS, or secondary progressive MS).

In the present study, we applied a highly specific inclusion approach, that is, we excluded patients without a diagnostic claim before an IFN β -1a prescription. This is standard practice in claims databases to select patients on the basis of a diagnosis and a treatment. This practice increases the robustness of the sample with regards to the target indication and allows better estimation of disease duration. However, in some cases, using

this method can lead to an underestimation of the total sample size because of missing diagnostic data in the inclusion time frame considered.

The identification of a relapse episode was based on a validated algorithm previously used.²⁸ However, this algorithm is based on treatment received, and the threshold for intervention may vary among clinicians. Therefore, the true number of relapses may be underestimated. IFN β -1a SC tiw use in health care claims data was assumed based on prescription fill date. It cannot be confirmed that a patient actually took the drug or took the drug as prescribed for the entire span of the prescription period (as measured by the days' supply calculation).

The database used consists of medical and pharmaceutical claims submitted by health care providers to insurance companies for reimbursement. Such claims are subject to possible coding errors and undercoding. Milder and more transient AEs (e.g., myalgia, arthralgia, dizziness, and injection-site reactions) may be underrepresented in claims databases due to misdiagnosis or undercoding, since it is the health care provider's decision whether or not to report the event in the health care claim.

As with other database studies, a limitation of this study is that no causal relationship between exposure to the drug product and a particular AE can be definitively determined. In addition, we did not directly control for the possible confounding effects of existing comorbidities on study results. However, we did measure the CCI at baseline. Results showed that 71.7% of study participants had a CCI score of 0 (i.e., no comorbidity). Given that this was intended as a real-world descriptive study in which AE information from phase III pivotal trials and passive, postmarketing surveillance data were compared with AE reports from real-world clinical practice, the greater the adjustment for confounding, the less representative the study becomes in terms of the real-world experience of patients receiving IFN β -1a SC tiw. As such, it is also possible that the IRs reported here were overestimated, although any such overestimation would not be expected to have a large effect on results.

The role of patient adherence to treatment is an important variable in the safety profile of IFN β -1a SC tiw. However, it was not the goal of this study to address this specific question, as the purely observational design led to highly different groups of adherent and nonadherent patients with respect to nonmodifiable outcomes (gender, age, and disease severity). In such a study, emphasis should be given to modifiable outcomes, in order to provide the health care providers with operational guidance on how to improve specific adverse events. More research is currently being conducted in this area.

As a further point regarding external validity, generalizability of findings beyond the United States is limited because of differences in MS patient demographics, health care treatment practices, and diagnostic criteria.

Postmarketing Safety Profile of Subcutaneous Interferon Beta-1a Given 3 Times Weekly: A Retrospective Administrative Claims Analysis

Conclusions

This study provides additional information concerning the safety profile of IFN β -1a SC tiw as used under real-world clinical care conditions. Administrative claims database studies are important in order to assess whether safety results seen in clinical trials with selected patient groups and tightly defined clinical care procedures apply to unselected patient populations treated in daily practice. Overall, our study results support the safety profile as described in the Warnings and Precautions, Adverse Reactions, and Postmarketing Experience sections of the U.S. PI for IFN β -1a SC tiw.

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DISCLOSURES

This study was commissioned and funded by EMD Serono, Inc., Rockland, Massachusetts (a subsidiary of Merck KGaA, Darmstadt, Germany) as part of its proactive pharmacovigilance operations. Samuelson is an employee of EMD Serono; Smith and Trochanov were employees at the time of this study. Sabidó-Espin, Guedes, Trochanov, and Richy are employees of Merck KGaA. Corvino was commissioned to perform the analytics of the study by EMD Serono.

The Truven MarketScan Commercial and Medicare data from 2006 to 2012, inclusive, have been licensed by Genesis Research on behalf of Merck KGaA.

Study concept and design was contributed by Smith, Corvino, and Sabidó-Espin. Data collection was performed by Corvino, Richy, and Sabidó-Espin. All authors contributed equally to data interpretation. The manuscript was written primarily by Smith, with assistance from Corvino and Sabidó-Espin.

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Postmarketing Safety Profile of Subcutaneous Interferon Beta-1a Given 3 Times Weekly: A Retrospective Administrative Claims Analysis

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**Postmarketing Safety Profile of Subcutaneous Interferon Beta-1a Given 3 Times Weekly:
A Retrospective Administrative Claims Analysis**

APPENDIX A Exposure of Interest Codes

Multiple Sclerosis

ICD-9-CM Code	Description
340	Multiple sclerosis

IFN β -1a SC tiw

National Drug Code	Product Name	Manufacturer	Generic Name
44087002203	SC-IFN β -1a Rebif	EMD Serono, Inc.	Interferon beta-1a
44087004403	SC-IFN β -1a Rebif	EMD Serono, Inc.	Interferon beta-1a
44087018801	SC-IFN β -1a Rebidose Titration Pack	EMD Serono, Inc.	Interferon beta-1a
44087332201	SC-IFN β -1a Rebidose	EMD Serono, Inc.	Interferon beta-1a
44087334401	SC-IFN β -1a Rebidose	EMD Serono, Inc.	Interferon beta-1a
44087882201	SC-IFN β -1a Rebif	EMD Serono, Inc.	Interferon beta-1a

Note: Diagnoses (in ICD-9-CM format) used to identify adverse event of interest appear in Appendix B.

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; IFN β -1a SC tiw = interferon beta-1a administered subcutaneously 3 times weekly.

APPENDIX B MedDRA Preferred Terms, System Organ Classes, and Corresponding ICD-9-CM Codes for Adverse Events in Warnings and Precautions, Adverse Reactions, and Postmarketing Experience Sections of U.S. Prescribing Information for IFN β -1a SC tiw^a

Outcomes of Interest	ICD-9-CM Codes
Blood and lymphatic system disorders	
Leukopenia	288.50
Neutropenia	288.0
Lymphopenia	288.51
Anemia	280, 281, 282, 283, 284, 285
Thrombocytopenia	287.3, 287.4, 287.5
Pancytopenia	284.1
Thrombotic microangiopathy	446.6
Hemolytic uremic syndrome	283.11
Thrombotic thrombocytopenic purpura	287
Lymphadenopathy	289.3, 785.6
Central and peripheral nervous system disorders	
Convulsions	780.3
Hypoesthesia	371.81
Muscle spasm	728.85
Parasthesia	782.0
Difficulty walking	719.7
Musculoskeletal stiffness	719.5
Seizures	340.0, 345, 345.0, 345.2, 345.3, 345.4, 345.5, 345.9, 780.30, 780.31, 780.39
Hypertonia	358
Coordination abnormal	781.3
Endocrine disorders	
Thyroid disorder	240, 241, 242, 243, 244, 245, 246
Hypothyroidism	243, 244
Hyperthyroidism	242.9
Eye disorders	
Retinopathy	362.0, 362.1, 362.2
Cotton wool spots	362.83
Retinal artery occlusion	362.31
Retinal vein occlusion	362.35
Vision abnormal	368
Vision impaired	369
Xerophthalmia	264.6

**Postmarketing Safety Profile of Subcutaneous Interferon Beta-1a Given 3 Times Weekly:
A Retrospective Administrative Claims Analysis**

APPENDIX B MedDRA Preferred Terms, System Organ Classes, and Corresponding ICD-9-CM Codes for Adverse Events in Warnings and Precautions, Adverse Reactions, and Postmarketing Experience Sections of U.S. Prescribing Information for IFN β -1a SC tiw^a (continued)

General disorders and administration site	
Headache	784.0
Fatigue	780.79
Pyrexia	780.60, 780.61, 780.62, 780.63
Chills	780.64
Rigors	780.99
Chest pain	786.5
Hyperhidrosis	780.8
Malaise	780.7, 780.79
Injection-site disorders	
Injection-site necrosis	995.21
Injection-site reaction	999.39
Gastrointestinal disorders	
Abdominal pain	789.0
Xerostomia	527.7
Hepatobiliary disorders	
SGPT increased	790.4
SGOT increased	796.4
Hepatic function abnormal	573.8
Hepatitis	573.3
Autoimmune hepatitis	571.42
Severe liver injury	571
Hepatic failure	572.2
Bilirubinemia	277.4
Jaundice	782.4
Immune system disorders	
Anaphylactic reactions	999.4, 995.0, 995.6
Allergic reaction	995.27, 995.3
Musculoskeletal and connective tissue disorders	
Myalgia	729.1
Arthralgia	719.4
Drug-induced lupus erythematosus	710.0
Skeletal pain	733.99
Back pain	724.5
Psychiatric disorders	
Depression	296.2, 296.20, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26, 296.3, 296.30, 296.31, 296.32, 296.33, 296.34, 296.35, 296.36, 296.5, 296.50, 296.51, 296.52, 296.53, 296.54, 296.55, 296.56, 296.82, 311
Suicidal ideation	300.9
Suicide	300.9
Somnolence	780.09
Suicide attempt	E95
Renal and urinary disorders	
Micturition frequency	788.41
Urinary incontinence	788.3
Skin and subcutaneous tissue disorders	
Rash, erythematous	695
Rash, maculo-papular	696.2
Urticaria	708
Erythema multiforme	695.1, 695.10, 695.11, 695.12
Stevens-Johnson syndrome	695.13, 695.14
Quincke's edema	995.1
Pruritus	698

^aThe incidence rate for suicidal ideation was calculated using the same ICD-9-CM code (300.9, unspecified nonpsychotic mental disorder) as that for suicide; however, suicidal ideation cases were distinguished from those classified as suicide cases based on the presence of 1 or more claims in the database subsequent to the ICD-9-CM 300.9 claim. ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification; IFN β -1a SC tiw=interferon beta-1a administered subcutaneously 3 times weekly; MedDRA=Medical Dictionary for Regulatory Activities; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase.